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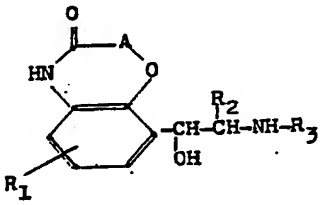
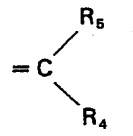
(71) Applicant
Boehringer Ingelheim International GmbH (FR Germany)
D-6507 Ingelheim am Rhein
Federal Republic of Germany
(72) Inventors
Armin Fugner
Ernst-Otto Renth
Anton Mentrup
Kurt Schromm
(74) Agents
Frank B Dehn
Imperial House
15-19 Kingsway
London WC2B 6UZ

(54) Benzo-heterocycles

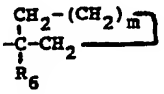
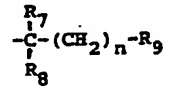
(57) Compounds of the formula



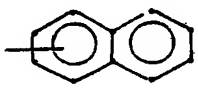
(A represents a single bond, $-CH_2-CH_2-$ or



R_4 represents hydrogen or alkyl, and R_5 represents hydrogen or alkyl or, when R_4 represents hydrogen, phenyl;
R_1 represents hydroxy, acyloxy, chlorine or hydrogen;
R_2 represents hydrogen, methyl or ethyl;
R_3 represents

 or 

m represents 2, 3 or 4,
n represents 1,2, or 3,
R_{6-8} represent hydrogen or methyl,
R_9 represents hydrogen, Ar, OAr, or $-NH-CO-Ar$,

 , 

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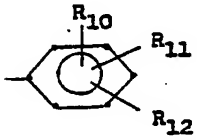


R_{10}, R_{11}, R_{12} are hydrogen, hydroxy, methyl, methoxy, halogen, $-CONH_2$ or $NH-R_{13}$, R_{13} is hydrogen, acyl or alkylsulfonyl, or any two of R_{10}, R_{11}, and R_{12} represent methylenedioxy), their acid addition salts, and corresponding compounds in which the CHOH group is replaced by CO (phenolic groups may be protected) are suitable for treating asthma, bronchitis, hay fever, cardiovascular disorders, for relaxation of the muscles of the uterus, and for improving flesh production and fodder utilisation in animals.

Certain of the chemical formulæ appearing in the printed specification were submitted after the date of filing, the formulæ originally submitted being incapable of being satisfactorily reproduced.

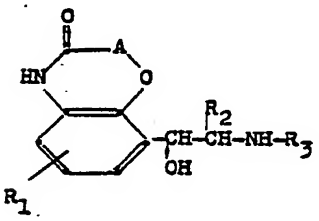
This print takes account of replacement documents later filed to enable the application to comply with the formal requirements of the Patents Rules 1978.

SPECIFICATION

Benzo Heterocycles

The invention relates to benzo heterocycles. More particularly it relates to benzo heterocycles having useful theraputic properties.

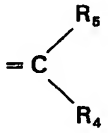
According to the invention, we provide compounds general formula (I)



(I)

wherein

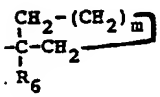
A represents a single bond, a group $-CH_2-CH_2-$, or a group



wherein R_4 represents hydrogen or lower alkyl, and R_5 represents hydrogen, or lower alkyl or, when R_4 represents hydrogen, a phenyl group;

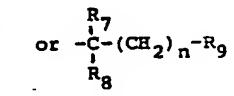
R_1 represents a hydroxy or acyloxy group or a chlorine or hydrogen atom;

R_2 represents hydrogen, or a methyl or ethyl group, and R_3 represents a group



(II)

or



(III)

wherein m represents either 2, 3 or 4,

n represents either 1, 2 or 3,

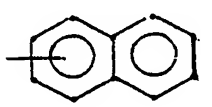
R_6 represents hydrogen or methyl,

R_7 represents hydrogen or methyl,

R_8 represents hydrogen or methyl,

and R_9 represents hydrogen, or a group Ar, –Oar, or –NH–CO–Ar,

wherein Ar represents one of the groups



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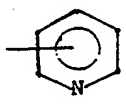

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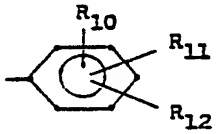


(IV)

in which R_{10}, R_{11}, and R_{12}, which may be the same or different, are each selected from hydrogen, hydroxy, methyl, methoxy, halogen, $-CONH_2$ and $NH-R_{13}$ the group R_{13} representing

hydrogen, acyl or a lower alkylsulfonyl group, or any two of R_{10}, R_{11} and R_{12} may represent a methylenedioxy group.

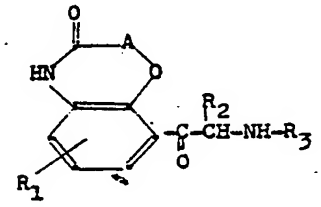
The compounds may occur in the form of racemates, enantiomers and possible diastereomeric pairs of enantiomers, as free bases or as acid additon salts, and all are included within the scope of this invention.

As used herein, the term "lower alkyl" denotes an alkyl group with 1 to 4 carbon atoms; the term "halogen" denotes fluorine, chlorine, bromine or iodine, preferably fluorine and chlorine, and the term "acyl" denotes an optionally substituted, optionally branched aliphatic acyl group with up to six carbon atoms or an optionally substituted benzoyl group.

Preferred are compounds of the invention wherein A represents a single bond, or a group $=CH_2$, $=CH(CH_3)$, $=(CH_3)_2$ or $=CH(C_2H_5)$,
R_1 represents hydroxy or acyloxy in the m- or p-position relative to the side-chain;
R_2 represents hydrogen or a methyl or ethyl group;
R_3 represents one of the groups of formula (II) or (III) above, in which
m represents 2 or 3,
n represents 1, 2 or 3,
R_6, R_7 and R_8 represent hydrogen or methyl,
R_9 represents hydrogen or a group Ar or NH–CO–Ar, wherein Ar represents a 2-pyridyl or 4-pyridyl group or a group of formula (IV), in which R_{10} represents hydrogen, hydroxy, methyl or a group $-NHR_{13}$, the group R_{13} representing acetyl or methanesulfonyl or, R_{10} together with R_{11} represents a methylenedioxy group,
R_{11} represents hydrogen, hydroxy, methyl or a group $-NHR_{13}$, the group R_{13} representing acetyl or methanesulfonyl or, together with R_{10}, represents a mthylenedioxy group,
R_{12} represents hydrogen.

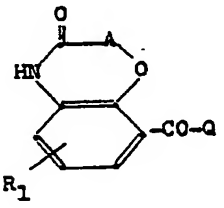
Particularly preferred are compounds wherein
A represents a group $=C(CH_3)_2$ or $-CH_2-$,
R_1 represents hydroxy in the p- or m-position relative to the side-chain,
R_2 represents hydrogen, or a methyl or ethyl group;
R_3 represents isopropyl, ter.-butyl, cyclopentyl,
l-methylcyclopentyl, or a group of formula (III) wherein n represents 1 or 2, R_7 and R_8 represent hydrogen or methyl,
and R_9 represents one of the groups phenyl, 4-hydroxyphenyl, 2-pyridyl, 4-pyridyl, 2-hydroxyphenyl, 2,6-dimethyl-4-hydroxy phenyl, 2-methyl-4-hydroxyphenyl,

According to a further aspect of the invention, we provide a process for the preparation of compounds of formula (I) as defined in claim 1 wherein either
a) a compound of formula (V)



(V)

wherein A, R_1, R_2 and R_3 are as defined in claim 1, any phenolic hydroxyl groups present being optionally protected by hydrogenolytically cleavable protecting groups, is reduced followed, if necessary by deprotection; or
b) a phenylglyoxal or hemiacetal of formula (XII)



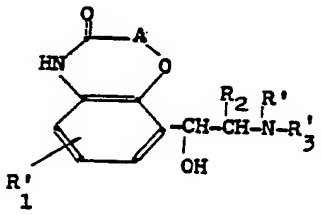
(XII)

wherein R_1 and A are as defined in claim 1, any phenolic hydroxy groups present being optionally protected by hydrogenolytically cleavable protecting groups, and Q represents –CHO or –CH(OH)–O–lower alkyl, is reacted under conditions of reductive amination with an amine of formula (XIII)

$H_2N–R_3$ (XIII)

wherein R_3 is as hereinbefore defined, any hydroxyl groups contained therein being optionally protected by hydrogenolytically cleavable protecting groups, followed, if necessary or if desired, by deprotection; or

c) deprotecting compound of formula (XVI)

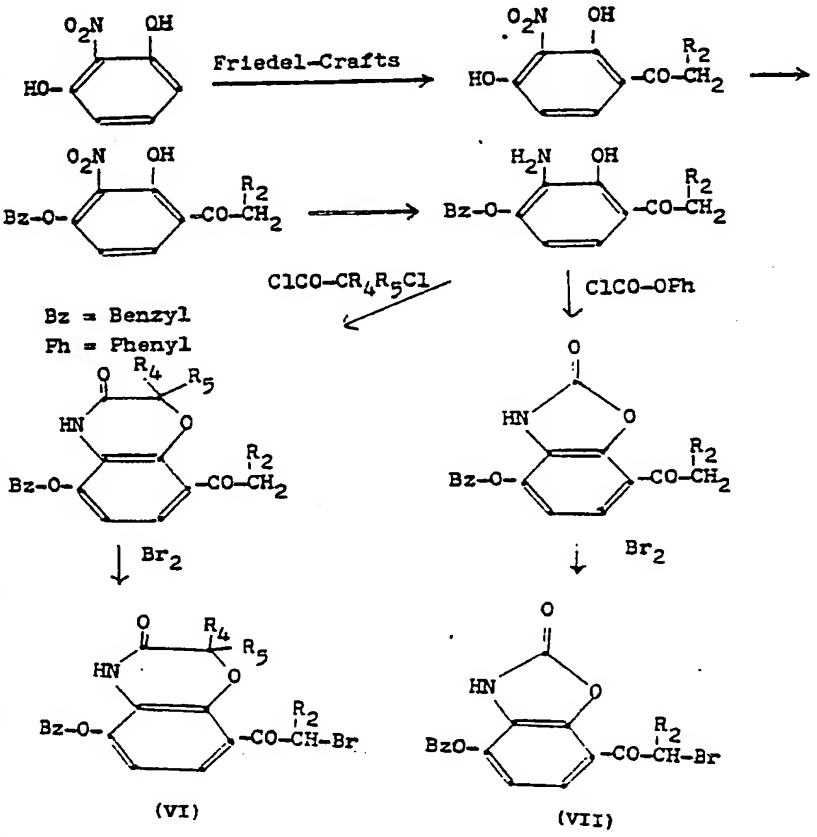


(XVI)

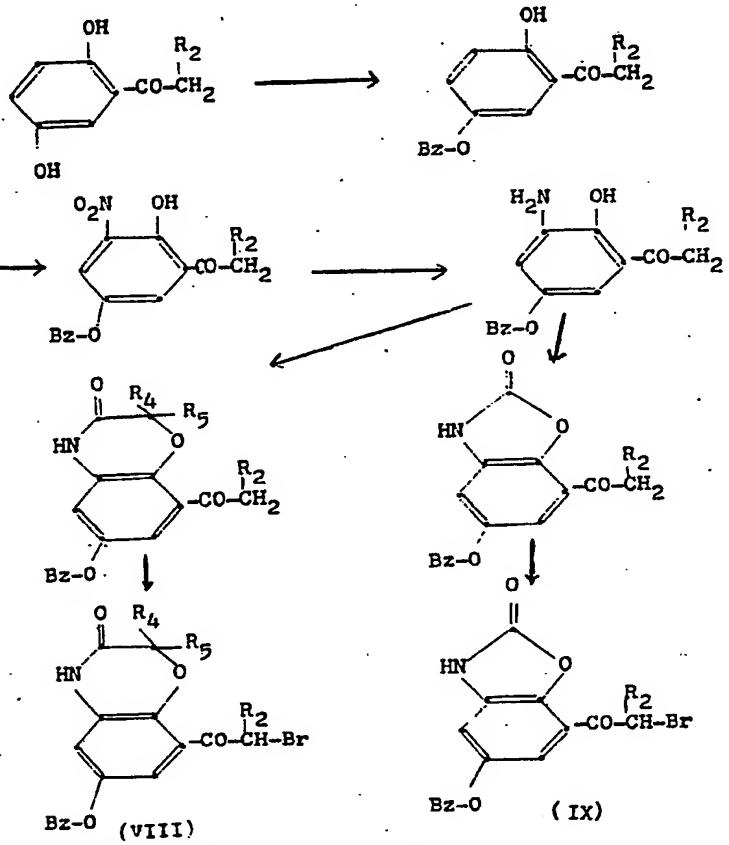
wherein A and R_2 are as defined in claim 1, R_1' represents R_1 or a hydroxyl group protected by hydrogenolytically cleavable protecting group, R_3' represents R_3, any hydroxyl group present in R_3 being optionally protected by a hydrogenolytically cleavable protecting group, and R' represents hydrogen or a hydrogenolytically cleavable protecting group, at least one protecting group which is to be split off being present in the compound of formula (XVI), after which, if necessary and if desired the compounds obtained according to reactions a) to c) are resolved by conventional methods into their enantiomers, optionally into diastereomeric pairs of enantiomers, any bases initially obtained are converted into their acid additon salts, and/or any acid addition salts initially obtained are converted into bases or salts of other acids.

In reaction a), the reduction is preferably effected in a solvent which is sufficiently stable under the reaction conditions, e.g. in a lower alcohol such as ethanol. As the reducing agents, water and hydrogenation catalysts (such as palladium, platinum, Raney nickel) or hydrides (such as sodium borohydride or diborane) may be used. By a suitable choice of reducing agent (catalytic reduction or reduction with hydrides) it is possible to prepare predominantly either the erythro- threo-form of an optically active compound of the invention. Any hydrogenolytically cleavable protecting groups present on the nuclear amino group or on a phenolic hydroxyl group, such as benzyl or substituted benzyl group, may be removed in the usual way during or after the reduction reaction.

The compounds of formula (V) used as starting materials which new compounds may be obtained according to methods known *per se*, as shown in the following reaction scheme, which is by way of example:

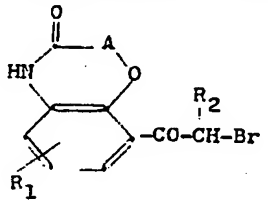


Corresponding bromoketones with an optionally protected hydroxyl group in the m-position relative to the side-chain may be obtained by the following reaction procedure, which is also by way of example:



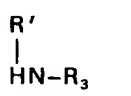
(VIII) (IX)

The bromoketones of formula (X)



(X)

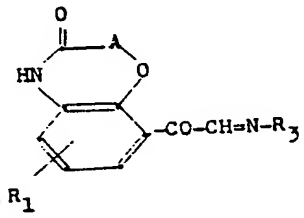
obtained in this way or by other conventional methods, wherein A, R_1 and R_2 are as hereinbefore defined but wherein phenolic hydroxyl groups may be protected by hydrogenolytically removable groups, such as benzyl, may then be converted into the compounds of formula (V) by reaction thereof with amines of formula



(XI)

wherein R_3 is as hereinbefore defined and R' represents hydrogen or a hydrogenolytically cleavable group, such as benzyl or substituted benzyl. The reaction is preferably carried out in suitable inert solvents such acetonitrile or ethyl acetate, in the presence of an acid-binding agent, such as sodium carbonate or excess amine. Any protecting groups present in the reacton product may be removed subsequently or as the reaction continues.

In reaction (b), instead of reagents of formulae (XII) and (XIII), it is also possible to reduce the Schiff bases of formula (XIV)



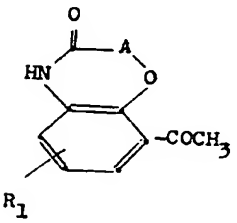
(XIV)

wherein A, R_1 and R_3 are as hereinbefore defined, which may occur as intermediates during the reaction.

Complex hydrides, preferably sodium borohydride or hydrogen and a hydrogenation catalyst such as platinum, palladium or nickel may be used as the reducing agent.

Any phenolic hydroxy groups contained in the starting materials may be protected by means of conventional hydrogenolytically cleavable groups. These protecting groups may be removed by hydrogenolysis in the usual way during or after the reduction.

The final products of this reaction are compounds of formula (I) wherein R_2 represents hydrogen. The compounds of formula (XII) used as starting materials may be obtained from acetophenone derivatives of formula (XV)



(XV)

wherein R_1 and A are as hereinbefore defined, by oxidation e.g. with selenium dioxide in aqueous dioxan. Depending on whether the product is crystallised from water or lower alcohols, either glyoxals or hemiacetals are obtained.

The amines of formula (XIII) are known or may readily be obtained according to conventional methods.

In reaction (c), the compounds of formula (XVI) may be obtained by reducing compounds of formula (V) by a process as described above. Examples of hydrogenolytically cleavable protecting groups include, in particular, benzyl and substituted benzyl.

If desired, the compounds obtained according to reactions (a) to (c) may be resolved into their enantiomers, optionally into diastereomeric pairs of enantiomers, by conventional methods. Any bases initially obtained may be converted into their acid addition salts, and/or any acid addition salts initially obtained may be converted into bases or salts of other acids.

The compounds according to the invention have pharmaceutical application. They have, *inter alia*, a broncholytic, spasmolytic and antiallergic activity and they increase ciliary activity and reduce inflammatory exudative reactions. They are therefore suitable for use in all forms of

asthma and bronchitis, and in urticaria, conjunctivitis, hay fever and colds and chills. They also act as relaxants on the muscles of the uterus and are therefore capable of minimising labour pains. The compounds may also be used for the treatment of cardiovascular disorders, e.g. high blood pressure, diseases of the peripheral blood vessels and arrhythmia. Further activities which have been observed are inhibition of gastric secretion and antidepressant effects in the CNS.

According to the further aspect of the invention, we provide pharmaceutical compositions comprising a compound of formula (I) as defined above in association with a carrier, excipient or diluent.

The therapeutic and prophylactic dosage suitable depends on the nature and gravity of the complaint and the method of adminstration.

In adults, the following dosages are recommended for the following indications.

As broncholytics, the compositions may be taken orally in a dosage of from 0.05 to 5 mg; by inhalation from 0.01 to 1.0 mg; and subcutaneously from 0.02 to 0.05 mg.

When used as uterine agents, the pharmaceutical compositions may be taken orally in a dosage of from 10 to 50 mg or, in the form of a solution for infusion, 10 ml ampoules containing from 0.01 to 1 mg may be used.

For vasolidation, 20 to 100 mg may be taken orally or ampoules containing 20 to 40 mg are used for i.m. injection. The hypotensive agents should preferably be taken orally in a dose of from 200 mg to 1.8 g.

The pharmaceutical compositions may also contain other therapeutic ingredients. Thus, the broncholytics can be combined with theophyllines, parasympatholytics (e.g. ipratropium bromide), secretolytics (e.g. bromhexine), musculotropic spasmolytics (e.g. papaverine), corticosteroids and antiallergics. In the uterus relaxants, combinations with corticoids are possible.

The compositions may take the form of capsules, tablets, solutions and suspensions which are suitable for oral administration. In pulmonary administration, dry powders preferably with a particle size diameter of from 0.5 to 7μ are introduced into the bronchial region by means of aerosol propellents. For parenteral administration, the compositions are preferably in the form of sterile isotonic aqueous solutions. For topical use, lotions, creams, ointments, emulsions and sprays may be used. Methods of preparing and formulating such compositions are known *per se*.

The compounds according to the invention may also be used to increase the growth rate of meat-producing animals, e.g. pigs, cattle, sheep, chickens and geese. The utilisation of fodder is improved substantially and furthermore the meat obtained is of higher quality and has a lower fat content than that obtained when the compounds of the invention are not used.

Aspects of the invention will now be illustrated in the following Examples, which should not be considered as limiting.

Pharmaceutical Examples

Tablets

Composition of a tablet

Active substance according to invention	20 mg
Colloidal silicic acid	10 mg
Lactose	118 mg
Potato starch	60 mg
Polyvinylpyrrolidone	6 mg
Na–cellulose glycolate	4 mg
Magnesium stearate	2 mg
	220 mg

Ampoules

Composition of the solution per ampoule

Active substance according to invention	10 mg
Sorbitol	40 mg
Distilled water *ad*	10 ml

Suppositories

Composition of each suppository

Active substance according to invention	100 mg
Suppository mass (cocoa butter)	1600 mg
	1700 mg

Powder for inhalation

Each hard gelatine capsule is packed with 0.5 mg of active substance according to the

invention and 19.5 mg of lactose with a particle diameter of between 0.5 and 7 μm.

For the pharmacological tests, the usual test methods and test animals or organs are used. From a pharmacological point of view the compounds according to the invention are, in some respects, very different from commercially available products used for the same indications. In addition to having a good duration of activity, they have a particularly sharp selectivity, for example, their broncholytic effect in relation to the increase in heart rate. Thus, for example, for the compound of Example 1, in guinea pigs the ED_{50}i.v. [μg/kg] of the increase in heart rate is more than ten times the ED_{50}i.v. [μg/kg] of broncholysis, which only 0.045 μg/kg. The resorption characteristics are generally favourable as well. Thus, the resorption quotient

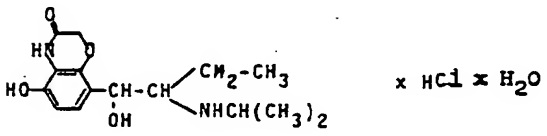
$$\frac{ED_{50}\text{p.o.}}{ED_{50}\text{i.v.}}$$

is only 1.1, for example, for compound 7 in Table 3, which means that the oral activity is virtually as great as the intravenous activity. In the mouse, for example, the LD_{50} values are so much higher than the therapeutic dose that a favourable therapeutic range is provided.

The following Examples illustrate the processes according to the invention more fully without restricting them, since the reaction conditions may be varied considerably with simialar results.

Depending on the solvent from which the substances mentioned hereafter are crystallised, some of them still contain defined quantities of the solvent bound in the crystal. The melting points given are uncorrected.

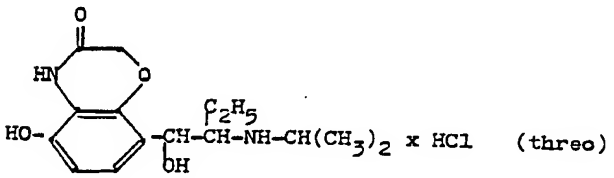
Example 1



16.1 g of 5′-benzyloxy-8′-(1-oxo-2-bromobutyl)-2H-1,4-benzoxazin-3-(4H)-one and 7.5 g of isopropylamine are stirred in 100 ml of acetonitrile for 4 hours at 60°C. After acidification with conc. hydrochloric acid and addition of the mixture to 100 ml of water 5′-benzyloxy-8′-(1oxo-2-isopropylamino-butyl)-2H-1,4-benzoxazin-3-(4H)-one hydrochloride (melting point 229–232°C) crystallises out. 6 g of these compounds are debenzylated in methanol, with the addition of palladium/charcoal as catalyst, to yield 5′-hydroxy-8′-(1-oxo-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one hydrochloride dihydrate (melting point 242–245°C).

By hydrogenating 3.3 g of this compound in methanol with platinum as catalyst, 3 g of erythro-5′-hydroxy-8′-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one hydrochloride hydrate are obtained (yield: 90% of theory), which melts at 208–210°C.

Example 1a



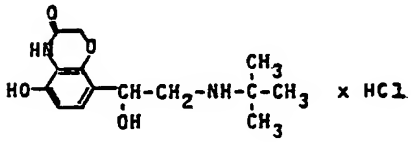
32.4 g of 5′-benzyloxy-8′-(1-oxo-2-bromo-butyl)-2H-1,4-benzoxazin-3-(4H)-one and 72 g of benzylisopropylamine are stirred at 100°C for 15 hours. After the addition of water the oil precipitated is taken up in ether and diluted with petroleum ether; crystallisation of 5′-benzyloxy-8′-(1-oxo-2-benzylisopropylamino-butyl)-2H-1,4-benzoxoazin-3-(4H)-one takes place.

11.6 g of this compound are combined with a mixture of 60 ml of ethanol and 60 ml of acetonitrile with 1 g of sodium borohydride and the resulting mixture is stirred for three hours. Then 250 ml of ice-cold water and 100 ml of ethyl acetate are added and, after the sodium

borohydride has been decomposed with concentrated acetic acid, with stirring, the mixture is made alkaline by the addition of concentrated ammonia solution, the ethyl acetate phase is separated off, dried and concentrated by evaporation in the Rotavapor. The oily residue is dissolved in ether and cooled and the threo-5′-benzyloxy-8′-(1-hydroxy-2-benzylisopropylamino-butyl)-2H-1,4-benzoxazin-3-(4H)-one precipitated (melting point 89–92°C) is suction filtered.

4.8 g of this compound are hydrogenated in 100 ml of methanol with palladium/charcoal as catalyst. After uptake has ended, the catalyst is removed from suction filtering, the mother liquor is concentrated by evaporation in the Rotavapor and the oily residue is dissolved in acetone/ethanol and acidified with the calculated quantity of hydrochloric acid. The solution is diluted with ether and the threo-5′-hydroxy-8′-(1-hydroxy-2-isopropylamino-butyl)-2H-1,4-benzoxazin-3-(4H)-one hydrochloride precipitated (yield: 74% of theory) is suction filtered; after being re-precipitated from methanol/ether it melts at 202–205°C.

Example 2



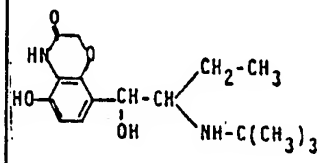
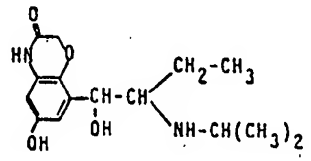
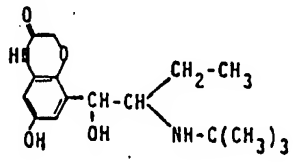
10 g of 5′-benzyloxy-8′-(1-oxo-2-bromo-ethyl)-2H-1,4-benzoxazin-3-(4H)-one and 8.75 g of benzyl-tert.-butylamine and refluxed in 100 ml of acetonitrile for 3 hours. After cooling, the crystals precipitated are suction filtered and washed with 200 ml of warm water. The crystals are acidified in acetonitrile with etheric hydrochloric acid; after dilution with ethyl acetate, 5′-benzyloxy-8′-(1-oxo-2-benzyl-tert.-butylaminoethyl)-2H-1,4-benzoxazin-3-(4H)-one hydrochloride is precipited (melting point 185–189°C).

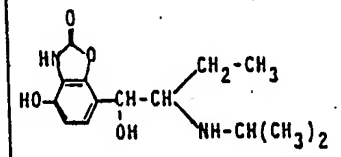
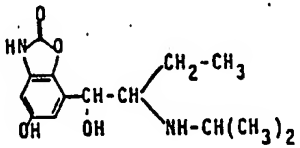
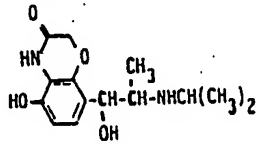
7 g of this compound are debenzylated at 5 bar and at 50°C in 100 ml of methanol, with the additon of palladium/charcoal as catalyst, to yield 5′-hydroxy-8′-(1-oxo-2-tert.-butylamino-ethyl)-2H-1,4-benzoxazin-3-(4H)-one hydrochloride (melting point 237–240°C).

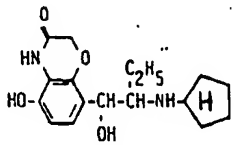
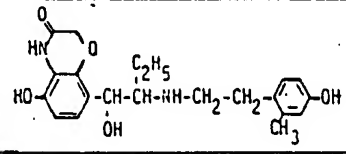
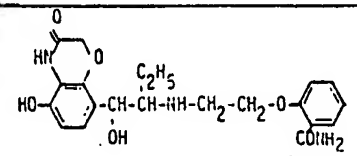
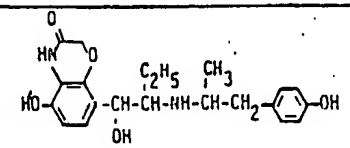
By catalytic hydrogenation of 2.2 g of this compound in methanol with platinum, 1.6 g of 5′-hydroxy-8′-(1-hydroxy-2-tert.-butylamino-ethyl)-2H-1,4-benzoxazin-3-(4H)-one hydrochloride are obtained (yield: 72.5% of theory), melting at 185–187°C.

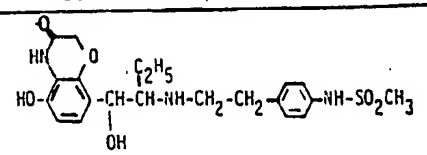
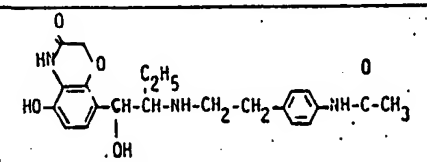
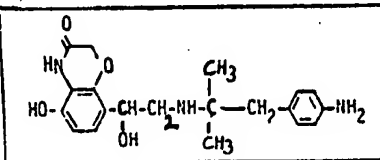
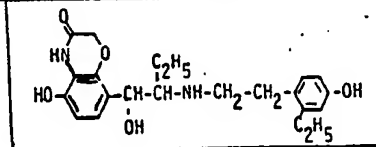
The following were synthesised as described in the Examples mentioned:

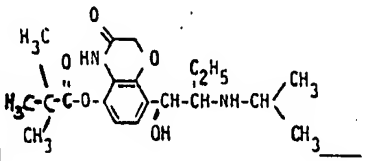
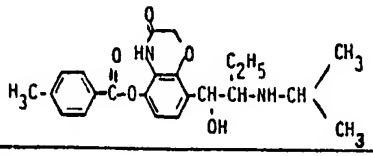
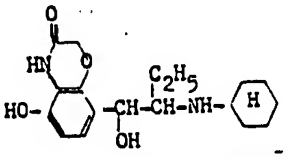
TABLE 1

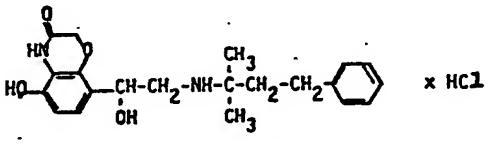
No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
1		66	Hydrochloric Acid x 2 Water	230 (decomp.)
2		63	Hydrochloric Acid	163 - 165
3		83	Hydrochloric Acid	259 - 261

No.	Structural formula	Yield % of theory	Salt with	Melting point °C
4		67	Hydrochloric Acid	230 - 232
5		71	Hydrochloric Acid x 1 Water	256 - 259
6		88	HCl x 1/2 H_2O	244

No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
7		86	HCl x 1/2 H_2O	243-245
8		73.5	HCl	206-209
9		52	HCl	170-173
10		64	CH_3SO_3H x H_2O	197-201

No.	Structural formula	Yield % of theory	Salt with	Melting point °C
11		83	CH_3SO_3H	187-190
12		54	HCl	208-211
13		70	HCl	155-159
14		90	HCl $CH_3SO_3H \times H_2O$	234-236 92-94

No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
15				
16				
17		90	HCl CH_3SO_3H x H_2O	234–236 92–94

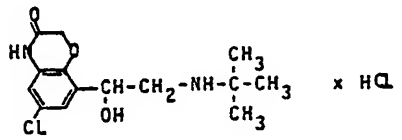


5 g of 5'-benzyloxy-8'-(1-oxo-2-hydroxy-2-ethoxy ethyl)-2H-1,4-benzoxazin-3-(4H)-one, 2.2 g of 1,1-dimethyl-3-phenylpropylamine and 50 ml of alcohol are heated to 50–60°C for 3 hours. After the reaction mixture has been cooled, the Schiff base precipitated (melting point 138–140°C) is suction filtered.

4.5 g of this compound are added to 100 ml of alcohol and mixed with 1 g of sodium borohydride and the mixture is stirred for 2 hours at ambient temperature. After the addition of 100 ml of water the 5'-benzyloxy-8'-[1-hydroxy-2-(4-phenyl-2-methyl-butylamino)-ethyl]-2H-1,4-benzoxazin-3-(4H)-one precipitated (melting point 162–164°C) is suction filtered and the hydrochloride (melting point 205–207°C) is prepared using etheric hydrochloric acid.

By catalytic hydrogeneration of this compound in 50 ml of methanol under normal conditions, using palladium charcoal as catalyst, 2.7 g of 5'-hydoxy-8'-[1-hydroxy-2-(4-phenyl-2-methyl-butylamino)-ethyl]-2H-1,4-benzoxazin-3-(4H)-one-hydrochloride are obtained (melting point 159–161°C, yield: 90% of theory).

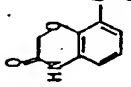
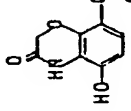
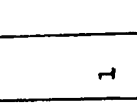
Example 4

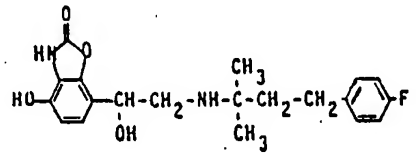
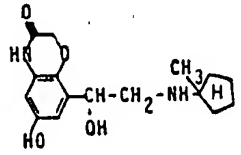
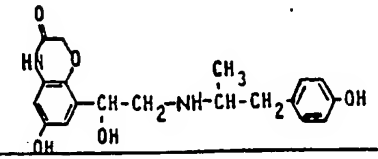


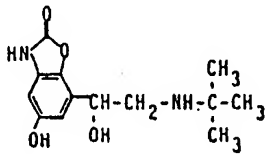
5.8 g of 6'-chloro-8'-(1-oxo-2-hydroxy-2-ethoxy-ethyl)-2H-1,4-benzoxazin-3-(4H)-one, 1.5 g of tert.-butylamine, 60 ml of dioxan and 60 ml of alcohol are heated to 50°C for 2 hours. The solution is then cooled and 2 g of sodium borohydride are added thereto at 10 to 20°C. The solution is stirred at ambient temperature for 1 hour, then poured on to 500 ml of ice-cold water and 150 ml of ethyl acetate are added. After the sodium borohydride has been decomposed with conc. acetic acid, with stirring, the mixture is made alkaline with aqueous amonia, the ethyl acetate phase is separated, dried with sodium sulphate and concentrated by evaporation in the Rotavapor. The oily residue is dissolved in 15 ml of alcohol, acidified with etheric hydrochloric acid and the 6'-chloro-8'-[1-hydroxy-2-(tert.-butylamino)-ethyl]-2H-1,4-benzoxazin-3-(4H)-one-hydrochloride precipitated (yield: 38% of theory) is suction filtered. After being re-precipitated twice from methanol, with the additon of active charcoal, the substance has a melting point of over 300°C (melting point of base: 173–177°C).

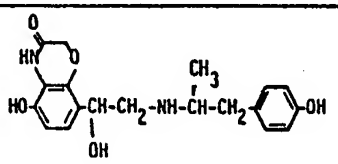
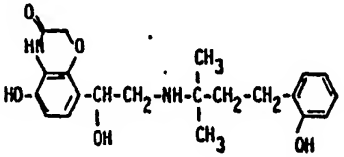
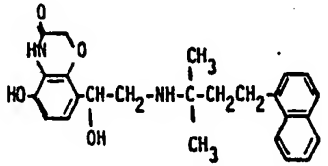
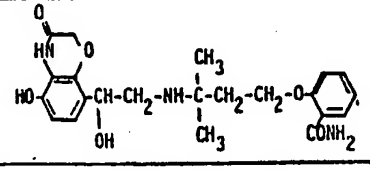
The following compounds were prepared analogously:

TABLE II

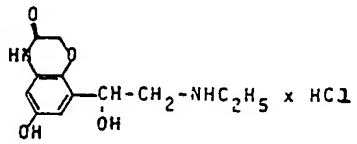
No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
1		40	Hydrochloric Acid	252 - 255
2		39	Hydrochloric Acid	185 - 187
3		40	Hydrochloric Acid x 1 ethanol	205 - 208

No.	Structural Formula	Yield % of theory	Salt with	Melting point °C.
4		42	Hydrochloric Acid x 1/2 water	155 - 160
5		52	Hydrochloric Acid	226 - 229
6		16	Hydrochloric Acid	206 - 209

No	Structural Formula	Yield % of theory	Salt with	Melting point °C
7		26	Hydrochloric Acid x 1 acetonitrile	Imprecise 195°C Decomp.

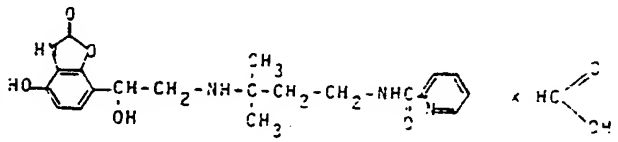
No.	Structural Formula	Yield %	Salt with	Melting point °C
8		42	HCl x CH_3OH	130-133
9		48	HCOOH x H_2O	120-124
10		40	CH_3SO_3H	192-195
11		35	HCl	205-208

Example 5



4.3 g of 5′-benzyloxy-8′-(1-hydroxy-2-benzylethylamino-ethyl)-2H-1,4-benzoxazin-3-(4H)-one-hydrochloride (melting point 232–235°C) are hydrogenated in 125 ml of methanol with the addition of 0.5 g of 5% palladium/ charcoal. After the calculated quantity of hydrogen has been taken up, the catalyst is filtered off and the solution is distilled under reduced pressure. By triturating the residue with acetonitrile 2.5 g of 5′-hydroxy-8′-(1-hydroxy-2-ethylamino-ethyl)-2H-1,4-benzoxazin-3-(4H)-one-hydrochloride are obtained (yield: 86.7% of theory), which melts at 240 to 242°C after being re-precipitated from methanol/ether.

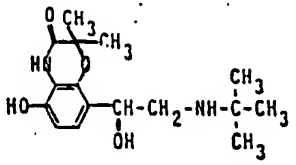
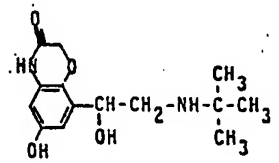
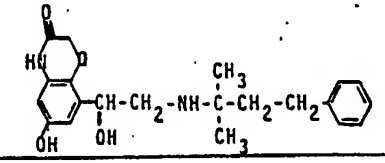
Example 6

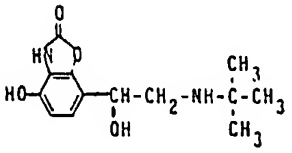
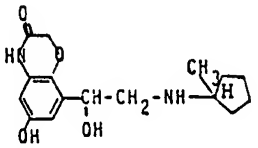
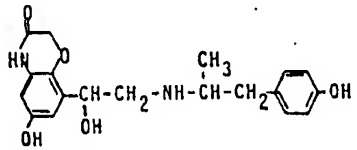


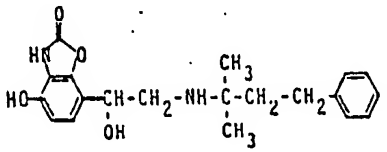
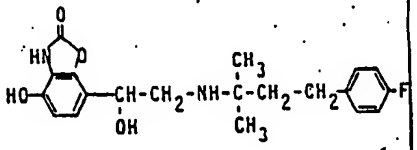
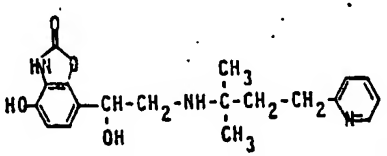
6.3 g of 4′-benzyloxy-7′-[1-hydroxy-2-(4-picolinic acid-amido-2-methyl-2-butylamino)-ethyl]-2-benzoxazolinone (melting point 130–133°C) are hydrogenated in 125 ml of methanol with the additon of 1 g of 5% palladium/charcoal. When the uptake of hydrogen has ended, the catalyst is filtered off and the clear solution is concentrated by evaporation in the Rotavapor under reduced pressure. The oily residue is dissolved in 10 ml of alcohol and 0.58 g of formic acid are added. After 5 hours, the 4′-hydroxy-7′-[1-hydroxy-2-(4-picolinic acid amido-2-methyl-2-butylamino)-2-benzoxazolinone-formate precipitated (yield: 78.5% of theory, melting point 166–168°C) is suction filtered.

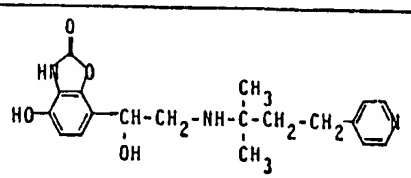
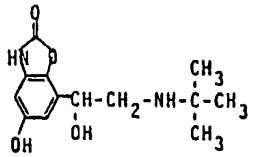
The following were synthesised according to the examples specified:

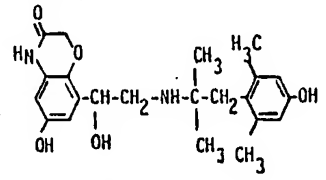
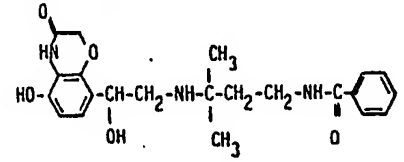
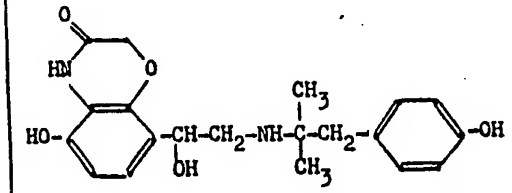
T A B L E III

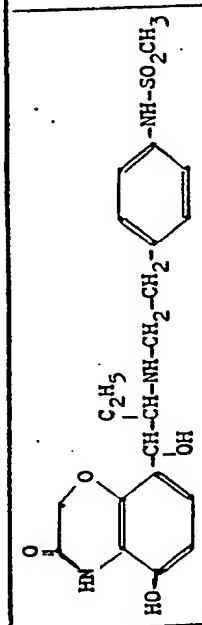
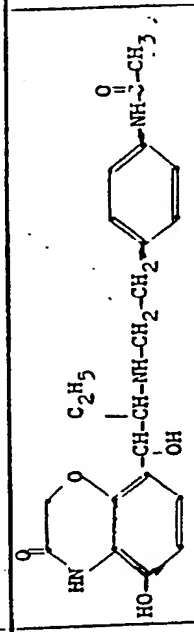
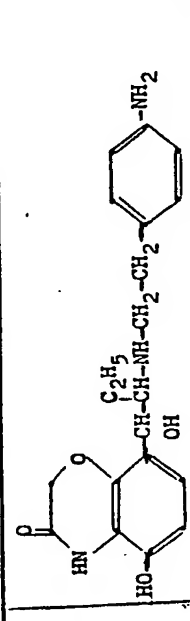
No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
1		87	Hydrochloric Acid x 1 ethanol	205 - 208
2		75	Hydrochloric Acid x 1 ethanol	246 - 247
3		70	Hydrochloric Acid x 1 ethanol	120 - 123

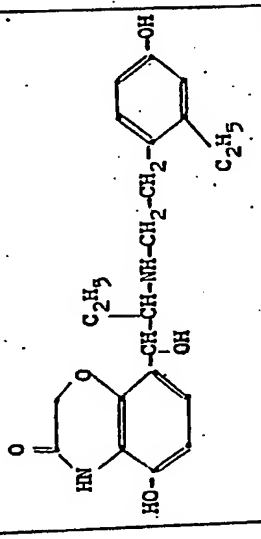
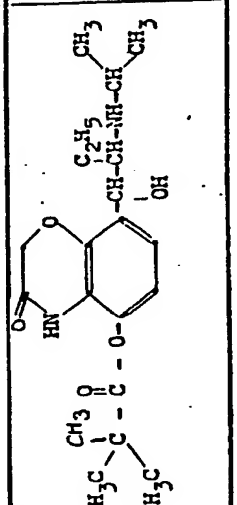
No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
4		70	Formic Acid x 1 water	189 - 192
5		88	Hydrochloric Acid	226 - 229
6		78.5	Hydrochloric Acid	206 - 209

No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
7		75	Hydrochloric Acid	174 - 175
8		90	Hydrochloric Acid x 1/2 Water	155 - 160
9		75	1/2 Fumaric Acid	175 - 178 (170-173 Base)

No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
10		60	Hydrochloric Acid	143 - 146
11		76	Hydrochloric Acid x 1 Acetonitrile	Imprecise 195 Decomp.

No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
12		91	CH_3SO_3H x 1 H_2O	252-254
13		71	CH_3SO_3H x 1/2 H_2O	178-180
14		72	HCl x 1,5 H_2O	159-162

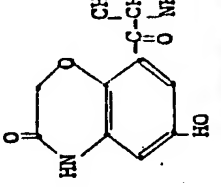
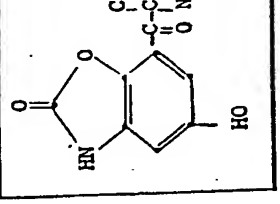
No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
15				
16				
17				

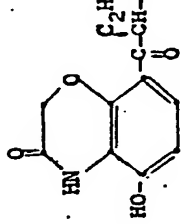
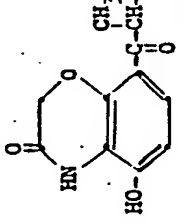
No.	Structural Formula	Yield % of theory	Salt with	Melting point °C
18				
19				

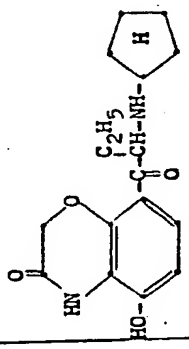
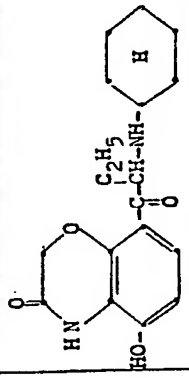
Intermediate products of formula (V) which can be obtained according to the above scheme are listed below.

The compounds of formula (V) may also be used as pharmaceutical compositions themselves, since they have similar pharmacological properties to the compounds of formula (I).

Formula	Salt with	Melting point °C
	HCl x $2H_2O$	240-242
	HCl	218-222
	HCl	250-254

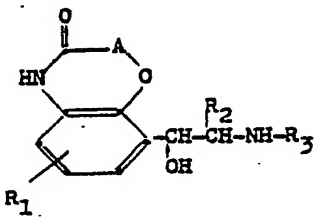
Formula	Salt with	Melting point °C
	HCl	250-253
	HCl	217-223

Formula	Salt with	Melting point °C
	HCl	156-161
	HCl	243-247

Formula	Salt with	Melting point °C
	HCl	254–258
	HCl	250

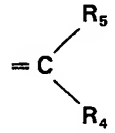
CLAIMS

1. Compounds of formula (I)

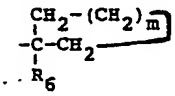


(I)

wherein
A represents a single bond, the group $-CH_2-CH_2-$, the group

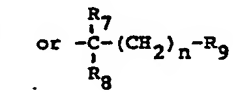


wherein R_4 represents hydrogen or a lower alkyl group, and R_5 represents hydrogen, or a lower alkyl or, when R_4 represents hydrogen, a phenyl group;
R_1 represents a hydroxy or acyloxy group or a chlorine or hydrogen atom;
R_2 represents hydrogen, or a methyl or ethyl group; and R_3 represents a group



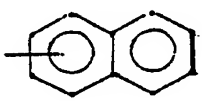
(II)

or

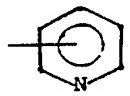


(III)

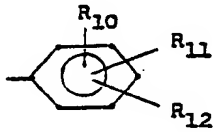
wherein m represents either 2, 3 or 4,
n represents either 1, 2 or 3,
R_6 represents hydrogen or methyl,
R_7 represents hydrogen or methyl,
R_8 represents hydrogen or methyl,
R_9 represents hydrogen, or a group Ar, OAr, or –NH– CO–Ar,
wherein Ar represents one of the groups



,



or



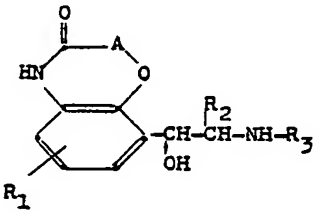
(IV)

in which R_{10}, R_{11}, R_{12} (which may be identical or different, each are selected from hydrogen, hydroxy, methyl, methoxy, halogen, $-CONH_2$ and $NH-R_{13}$, the group R_{13} representing hydrogen, acyl or a lower alkylsulfonyl group, or any two of R_{10}, R_{11} and R_{12} may represent a methylenedioxy group, the compounds being in the form of their racemates, enantiomers or diastereomeric pairs of enantiomers, or their acid addition salts.

2. Compounds of formula (I) as claimed in Claim 1 wherein A represents a single bond, or a group $=CH_2$, $=CH(CH_3)$, $=(CH_3)_2$ or $=CH(C_2H_5)$,
R_1 represents hydroxy or acyloxy in the m- or p-position relative to the side-chain;

R_3 represents hydrogen or a methyl or ethyl group;
R_3 represents one of the groups of formula (II) or (III), in which
m represents 2 or 3,
n represents 1, 2 or 3,
R_6, R_7 and R_8 represent hydrogen or methyl,
R_9 represents hydrogen or a group Ar or NH–CO–Ar, wherein Ar represents a 2-pyridyl or 4-pyridyl group or a group of formula (IV), in which R_{10} represents hydrogen, hydroxy, methyl or a group $-NHR_{13}$, the group R_{13} representing acetyl or methanesulfonyl, or, R_{10} together with R_{11} represents a methylenedioxy group,
R_{11} represents hydrogen, hydroxy, methyl or a group $-NHR_{13}$, the group R_{13} representing acetyl or methanesulfonyl, or, together with R_{10}, represents a methylenedioxy group,
R_{12}represents hydrogen.

3. Compounds of formula (I) as claimed in claim 1 wherein A represents a group $=C(CH_3)_2$ or $-CH_2-$;
R_1 represents hydroxy in the p- or m-position relative to the side-chain;
R_2 represents hydrogen, or a methyl or ethyl group;
R_3 represents isopropyl, tert.-butyl, cyclopentyl, 1-methylcyclopentyl, or a group of formula (III) wherein.
n represents 1 or 2, R_7 and R_8 represent hydrogen or methyl,
and R_9 represents one of the groups phenyl, 4-hydroxyphenyl, 2-pyridyl, 4-pyridyl, 2-hydroxy-phenyl, 2,6-dimethyl-4-hydroxy phenyl, 2-methyl-4-hydroxyphenyl,

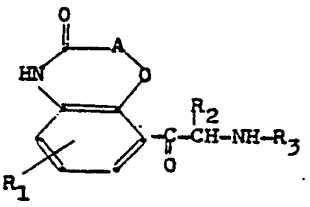


(I)

4. 5′-Hydroxy-8′-(1-hydroxy-2-isopropylamino-butyl)-2H-1,4-benzoxazin-3-(4H)-one and salts thereof.

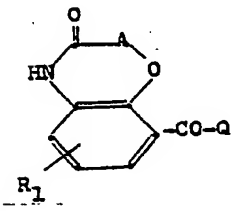
5. Pharmaceutical compositions comprising a compound as claimed in any one of claims 1 to 4 in association with a pharmaceutically acceptable carrier, diluent or excipient.

6. A process for the preparation of compounds of formula (I) as defined in claim 1 wherein either
a) a compound of formula (V)



(V)

wherein A, R_1, R_2 and R_3 are as defined in claim 1, any phenolic hydroxyl groups present being optionally protected by hydrogenolytically cleavable protecting groups, is reduced followed, if necessary by deprotection; or
b) a phenylglyoxal or hemiacetal of formula (XII)



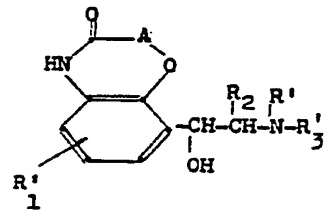
(XII)

wherein R_1 and A are as defined in claim 1, any phenolic hydroxy groups present being optionally protected by hydrogenolytically cleavable protecting groups, and Q represents –CHO or –CH(OH)–O–lower alkyl, is reacted under conditions of reductive amination with an amine of formula (XIII)

$H_2N–R_3$ (XIII)

wherein R_3 is as hereinbefore defined, any hydroxyl groups contained therein being optionally may be protected by hydrogenolytically cleavable protecting groups, followed, if necessary or if desired, by deprotection; or

c) deprotecting compound of formula (XVI)



(XVI)

wherein A and R_2 are as defined in claim 1, R'_1 represents R_1 or a hydroxyl group protected by a hydrogenolytically cleavable protecting group, R_3 represents R'_3 any hydroxyl group present in R_3 being optionally protected by a hydrogenolytically cleavable protecting group, and R′ represents hydrogen or a hydrogenolytically cleavable protecting group, at least one protecting group which is to be split off being present in the compound of formula (XVI), after which, if necessary and if desired the compounds obtained according to reactions a) to c) are resolved by conventional methods into their enantiomers, optionally into diastereomeric pairs of enantiomers, any bases initially obtained are converted into their acid addition salts, and/or any acid addition salts initially obtained are converted into bases or salts of other acids.

7. A process as claimed in claim 6 substantially as hereinbefore described.

8. A process as claimed in claim 6 substantially as hereinbefore described with reference to the Examples.

9. Compounds of formula (V) wherein A, R_1, R_2 and R_3 are as defined in claim 1.

10. A process for the preparation of compounds of formula (V) as defined in claim 9 substantially as hereinbefore described.

11. A process for the preparation of compounds of formula (V) as defined in claim 9 substantially as hereinbefore described with reference to the Examples.

12. Compounds of formula (I) as defined in claim 1 whenever prepared by a process as claimed in any of claims 6 to 8.

13. A method of treatment or prophylaxis of the human or animal body to combat asthma, bronchitis, urticaria, conjunctivitis, hay fever, colds, chills, labour pains and cardiovascular disorders or to relax the uterus which comprises administering to said body an effective amount of compound of formula (I) or formula (V) as defined in claim 1 or claim 9 respectively or a physiologically acceptable acid addition salt thereof.

14. Compounds of formula (I) (as defined in claim 1) and physiologically acceptable acid addition salts thereof for use in a method of treatment or prophylaxis of the human or animal body to combat asthma, bronchitis, urticaria, conjunctivitis, hay fever, colds, chills, labour pains and cardiovascular disorders or to relax the uterus.

15. Compositions for improving the production of flesh and the utilisation of fodder in meat-producing animals which contain a compound of formula (I) as defined in claim 1.

16. The use of compounds of formula (I) as defined in claim 1 for improving flesh production and the utilisation of fodder in meat-producing animals, particularly poultry, cattle, pigs and sheep.

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